Support for the amendments to the claims can be found throughout the specification and in the claims as originally filed.

No new matter has been added. Any cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Objections to the Disclosure

The Examiner has objected to the disclosure because, "[a]t page 3, line 27, "cholinesterase" is misspelled.

Applicants have amended the disclosure to correct the foregoing misspelling of the word cholinesterase. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this objection.

Rejection of Claim 25 Under 35 U.S.C. § 112, Second Paragraph

The Examiner rejected claim 25 under 35 U.S.C. § 112, second paragraph because, "[a]t claim 25, line 2, 'or' should be changed to 'and' so that standard Markush language should be used."

Applicants respectfully submit that in view of the amendments to claim 25, the foregoing rejection has been rendered moot. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

Provisional Rejection of Claims 24-32 and 47 Under the Judicially Created Doctrine of Obviousness-Type Double Patenting

The Examiner has provisionally rejected claims 24-32 and 47 under the judicially created doctrine of obviousness-type double patenting as, "being unpatentable over claims 6, 7, and 15-17 of copending Application No. 09/519,019 in view of WO Patent Application 98/08868, Kroin et al. (U.S. Patent No. 5,776,939), and the WO Patent Application 95/20980."

Applicants respectfully submit that when the pending claims in the present application are indicated as allowable, Applicants will consider submitting, if appropriate, a terminal disclaimer complying with 37 C.F.R. §1.321 (b) and (c) which will obviate this rejection. The filing of this terminal disclaimer should in no way be construed as an acquiescence to the Examiner's obviousness-type double patenting rejection and will be done solely to expedite the prosecution of the application.

Rejection of Claims 24-32 and 47 as Not Being Patentably Distinct From Claims 6, 7, and 15-17 of USSN: 09/519,019

The Examiner has rejected claims 24-32 and 47 as not being patentably distinct from claims 6, 7, and 15-17 of commonly assigned application serial no. 09/519,019 (hereinafter "the '019 application").

In accordance with 37 C.F.R. § 1.78(c) and 35 U.S.C. § 132, Applicants submit herewith copies of the Assignment documents for the '019 application and for the instant application (see Appendices B-C, respectively) which show that, at the time the invention in the instant application was made, the inventions were commonly owned. Therefore, the '019 application does not qualify as 35 U.S.C. § 102(f), § 102(g), or § 102(e) prior art against the instant application. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

Provisional Rejection of Claims 24-32 and 47 Under 35 U.S.C. § 102(e)

The Examiner has provisionally rejected claims 24-32 and 47 under 35 U.S.C. § 102(e) over the '019 application. The Examiner is of the opinion that, "because the inventorship of copending application 09/519,019 is different than the inventorship of the instant application, and because copending application 09/519,019 has an earlier effective filing date than the instant application, copending application 09/519,019 is provisionally available as prior art against the instant claims under 35 U.S.C. § 102(e)."

Applicants have cancelled claim 47 thereby rendering this rejection, as it pertains to claim 47, moot.

As this rejection pertains to claims 24-32, Applicants respectfully traverse the rejection for the following reason. Although the inventors of the instant application and the '019 application are different, at the time the invention in the instant application was made, the inventions were commonly owned (see the executed Assignments submitted herewith). As these inventions were commonly owned at the time the invention was made, the '019 application is not available as 35 U.S.C. § 102(e) prior art against the instant application. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

Provisional Rejection of Claims 24-32 and 47 Under 35 U.S.C. § 103(a)

The Examiner has provisionally rejected claims 24-32 and 47 under 35 U.S.C. § 103(a) as " being obvious over copending Application No. 09/519, 019 which has a common assignee with the instant application in view of the WO Patent Application 98/08868, Kroin et al (U.S. Patent No. 5,776,939), and the WO Patent Application 95/20980." In particular, the Examiner is of the opinion that

> [b]ased on the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. § 102(e) if published or patented. This provisional rejection under 35 U.S.C. § 103(a) is based upon a presumption of future publication or patenting of the conflicting application.

Applicants have cancelled claim 47, thereby rendering this rejection, as it pertains to claim 47, moot.

As this rejection pertains to claims 24-32, Applicants respectfully traverse the rejection for the following reason. Applicants respectfully submit that, at the time the instant invention was made, the inventions disclosed in the '019 application and the instant application were commonly owned (as evidenced by the executed Assignments submitted herewith). Accordingly, the '019 application is not available as 35 U.S.C. § 102(e) or §103 art against the instant application. Accordingly, Applicants respectfully submit that the Examiner reconsider and withdraw the foregoing rejection.

Rejection of Claims 24, 25, 31, 32 and 47 Under 35 U.S.C. § 102(b)

The Examiner has rejected claims 24, 25, 31, 32, and 47 under 35 U.S.C. § 102(b) as, "being anticipated by the WO Patent Application 98/08868 in view of the Applicants' admission at page 11, lines 2-3 of the specification." In particular, the Examiner is of the opinion that

> [t]he WO Patent Application '868 teaches β-amyloid peptide derivatives which are administered in vivo to the CNS or across the BBB for the diagnosis and treatment of amyloidogenic diseases. Administration can be as a single bolus or several divided doses. Supplementary active compound can be incorporated into the compositions. Two or more of the β-amyloid peptide derivatives may be used in combination. Particularly exemplified β-amyloid peptide derivatives may be used in combination. Particularly exemplified β-amyloid peptide derivatives include PPI-558, PPI-578, PPI-655, and P[P]I-657. .... With respect to the teachings in the WO Patent Application '868 of the administration of a single β-amyloid peptide derivatives, Applicants admit at page 11, lines 2-3, that the β-amyloid peptide derivatives are themselves P-glycoprotein inhibitors. Accordingly, the teachings of the WO Patent Application '868 of the administration of a single β-amyloid peptide derivative constitute an inherent teaching of the administration of both a β-amyloid peptide derivative and a P-glycoprotein inhibitor. Note that the claims do not contain any limitations requiring the β-amyloid peptide derivatives and the P-glycoprotein inhibitors to be chemically distinct compounds. It follows then that the WO Patent Application '868's teaching of administering the β-amyloid peptide derivatives either as a single bolus or in several divided doses constitutes an inherent teaching of the simultaneous or non-simultaneous administration of a β-amyloid peptide derivative and a P-glycoprotein inhibitor. With respect to the teachings of the WO Patent Application '868 of the administration of two or more β-amyloid peptide derivatives in combination, again Applicants admit at page 11, lines 2-3, that β-amyloid peptide derivatives are themselves P-glycoprotein inhibitors. Accordingly, at least on of the β-amyloid peptide derivatives in the WO Patent Application '868's combination can be designated as corresponding to Applicants' β-amyloid peptide derivative, and at least one of the other β-amyloid peptide derivatives in the WO Patent Application '868's combination can be designated as inherently corresponding to Applicants' P-glycoprotein inhibitor.

Applicants have cancelled claim 47 thereby rendering this rejection, as it pertains to claim 47, moot.

As this rejection pertains to claims 24, 25, 31 and 32, Applicants respectfully traverse the rejection for the following reasons. As amended, claim 24 and claims depending therefrom are directed to methods for enhancing the bioavailability of a β-amyloid peptide derivative to the brain of a subject, comprising administering to the subject the β-amyloid peptide derivative and a P-glycoprotein inhibitor, ***wherein the P-glycoprotein inhibitor and the β-amyloid polypeptide derivative are separate chemically distinct compounds*** and wherein the P-glycoprotein inhibitor is not a liposome or Tween-80, thereby enhancing the bioavailability of the β-amyloid peptide derivative to the brain of the subject.

For a prior art reference to anticipate in terms of 35 U.S.C. §102 a claimed invention, the prior art must teach ***each and every element*** of the claimed invention. Lewmar Marine v. Barient, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

Applicants respectfully submit that the '868 application fails to teach or suggest methods for enhancing the bioavailability of a β-amyloid peptide derivative to the brain of a subject in which the P-glycoprotein inhibitor and the β-amyloid polypeptide derivative are chemically distinct compounds. Accordingly, the '868 application does not anticipate the pending claims and Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

Rejection of Claims 24, 25, 31, 32 and 47 Under 35 U.S.C. § 102(b)

The Examiner has rejected claims 24, 31, and 47 under 35 U.S.C. § 102(b) as, "being anticipated by the WO Patent Application 98/08868 in view of the WO Patent Application 95/20980." The examiner states

> [t]he WO Patent Application '868 at page 34, lines 30-33, teaches a preferred formulation comprising the β–amyloid peptide derivatives in combination with Tween-80, and at page 36, lines 7-10, teaches the β-amyloid peptide derivatives in combination with liposomes. The WO Patent Application '980 teaches that Tween-80 and liposomes are inherently P-glycoprotein inhibitors. Because the same active agents are being administered by the same method steps in the WO Patent Application '868 and in Applicants' claims, inherently the bioavailability of the β-amyloid peptide derivatives of the WO Patent Application '868

will be enhanced by the Tween-80 and the liposomes of the WO Patent Application '868 to the same extent claimed by Applicants.

Applicants have cancelled claim 47 thereby rendering this rejection, as it pertains to claim 47, moot.

As this rejection pertains to claims 24 and 31, Applicants respectfully traverse the rejection for the following reasons. As amended, claims 24 and claims depending therefrom are directed to methods for enhancing the bioavailability of a β-amyloid peptide derivative to the brain of a subject, comprising administering to the subject the β-amyloid peptide derivative and a P-glycoprotein inhibitor, ***wherein the P-glycoprotein inhibitor and the β-amyloid polypeptide derivative are separate chemically distinct compounds and wherein the P-glycoprotein inhibitor is not a liposome or Tween-80,*** thereby enhancing the bioavailability of the β-amyloid peptide derivative to the brain of the subject.

For a prior art reference to anticipate in terms of 35 U.S.C. §102 a claimed invention, the prior art must teach ***each and every element*** of the claimed invention. Lewmar Marine v. Barient, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

Applicants respectfully submit that the '868 application and the '980 application, alone or in combination, fail to teach or suggest methods for enhancing the bioavailability of a β-amyloid peptide derivative to the brain of a subject in which the P-glycoprotein inhibitor and the β-amyloid polypeptide derivative are separate chemically distinct compounds and in which the P-glycoprotein inhibitor is not a liposome or Tween-80. Accordingly, the '868 application and the '980 application, alone or in combination, fail to anticipate the pending claims and Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

Rejection of Claims 24, 25, 27-32 and 47 Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 24, 25, 27-32 and 47 under 35 U.S.C. § 103(a) as being, "obvious over the WO Patent Application 98/08868 as applied against claims 24, 25, 31, 32 and 47 and further in view of Kroin et al. (U.S. Patent No. 5,776,939) or the WO Patent Application 95/20980." The examiner states that

> [t]he WO Patent Application '868 discloses the desirability of oral administration of the β-amyloid peptide derivatives (see, e.g., page 33, lines 7-8) and discloses the desirability of the administration of the β-amyloid peptide derivatives so that they cross the blood-brain barrier (see, e.g., page 34, line 34-page 35, line 5), but does not recite co-administration of a P-glycoprotein inhibitor or a cytochrome P450 inhibitor in order to improve the oral administration or in order to increase the crossing of the blood-brain barrier. Kroin et al teach co-administration of drugs with a compound of Formula (c) so that the oral bioavailability of the drugs and the bioavailability of the drugs to the brain is enhanced. The compounds of Formula (C) are P-glycoprotein inhibitors. The compounds of Formula (C) are administered simultaneously or at different times. The WO Patent Application '980 teaches co-administration of an orally administered drug with an inhibitor of a cytochrome P450 3A enzyme and/or an inhibitor of P-glycoprotein-mediated membrane transport so that the bioavailability of the drug is increased. Cyclosporine, SDZ PSC-833 (i.e., valspodar), antiarrhythmics, antibiotics, antifungals, antiparasites, calcium channel blockers, cancer chemotheraperuics, hormones, local anesthetics, phinothiazines, and tricyclic antidepressants are disclosed as useful inhibitors. The drugs and inhibitors can be administered simultaneously or at different times. It would have been obvious to one of ordinary skill in the art at the time the Applicants' invention was made to co-administer the β-amyloid peptide derivatives of the WO Patent Application '868 with the P-glycoprotein inhibitor and/or the P450 inhibitors of Kroin et al or the WO Patent Application '980 because the methods of Kroin et al and the WO Patent application '080 would have been expected to be useful in aiding and increasing the oral administration and the crossing of the blood-brain barrier taught desirable by the WO Patent Application '868.

Applicants have cancelled claim 47 thereby rendering this rejection, as it pertains to claim 47, moot.

As this rejection pertains to claims 24, 25, and 27-32, Applicants respectfully traverse the rejection for the following reasons.

The Examiner has Failed to Provide the Necessary Motivation to Impel One of Ordinary Skill in the Art to Make Applicants' Invention

Applicants respectfully traverse the Examiner's assertion that the proposed combination of the above-cited references renders the claimed invention obvious to the

ordinarily skilled artisan at the time of the invention. Reconsideration and withdrawal of the rejection in light of the following discussion is respectfully requested.

It is Applicants' position that the teachings of the cited references relied upon by the Examiner to combine the references are legally insufficient to provide the requisite motivation. With regard to the necessary legal standard, Applicants refer the Examiner to *Arkie Lures v. Larew Tackle*, 119 F.3d 953, (Fed. Cir. 1997). In Arkie Lures, the Larew invention was directed to a "salt-impregnated fishing lure." In that case, the CAFC overturned the district court's finding of obviousness. The CAFC agreed that "[t]he use of salty bait to catch fish was known,[and] plastisol lures were known." *Id* at page 956. However, the CAFC found that although the literature on "fishing lures is apparently quite extensive, but despite the long use of salty lures and plastic lures, no reference was cited that showed or suggested this combination." The CAFC continued that "[t]he evidence showed the complexity of the plastic fishing lure art. Those in the field of the invention viewed Larew's invention not as a simple concept of adding salty taste to a known lure, but as a complex combination requiring experience of fishing and fishing lures and the technology of plastics." Id at page 957.

The court further stated that:

> No prior art showed or suggested the combination of a plastisol lure with salt, although the prior art was extensive as to the separate elements, and suggested including organic attractants in plastic lures. . . . The question is not whether salt "could be used," as the district court concluded, but whether it was obvious to do so in light of all the relevant factors. . . ***It is insufficient to establish obviousness that the separate elements of the invention existed in the prior art, absent some teaching or suggestion, in the prior art, to combine the elements***. Indeed, the years of use of salty bait and of plastic lures, without combining their properties, weighs on the side of unobviousness of the combination (emphasis added).

Id at pages 957 and 958.

Similar to the situation in the Arkie Lures case, the teachings of the cited references alone or in combination are ***insufficient*** to establish the obviousness of the claimed invention absent some teaching or suggestion in the art to combine and modify the teachings of those references to arrive at the claimed invention. The Examiner argues that the motivation would arise from the teachings of the '868 application about the desirability of oral administration of the β-amyloid peptide derivatives and the desirability of the administration of the β-amyloid peptide derivatives so that they cross the blood-brain barrier. However, the sections of the '868 application which the Examiner relies upon for this rejection also teach that the ***preferred way*** of administering the β-amyloid peptide derivatives is by ***intraspinal and intracerebral administration*** (see page 33, lines 4-6). Thus, the skilled artisan reading the foregoing sections of the '868 application would not have been motivated to use oral administration of the β-amyloid peptide derivatives and look for methods to enhance the ability of these compounds to cross the blood-brain barrier. Rather, based on the foregoing teachings of the '868 application, the skilled artisan would most likely be motivated to administer these compounds directly to the CNS by ***intraspinal*** or ***intracerebral administration***.

Even if the skilled artisan were motivated to look to methods for enhancing the ability of the β-amyloid peptide derivatives to cross the blood-brain barrier, which Applicants unequivocally dispute, the '868 application teaches a plethora of ways for successfully achieving this result which are different than using a P-glycoprotein inhibitor (see page 35, line 1 through page 36, line 23 of the '868 application). In fact, the '868 application never teaches or suggests the use of a P-glycoprotein inhibitor for this purpose.

In view of the foregoing, it is evident that the '868 application fails to provide the requisite teaching or suggestion which would motivate the ordinarily skilled artisan to co-

administer to a subject a β-amyloid peptide derivative and a P-glycoprotein inhibitor, as required by Applicants' claims.

In further support of their position, Applicants point to the recent CAFC decision in *In re Rouffet* (*In re Rouffet*, 149 F.3d 1350, 47 USPQ.2d 1453 (Fed. Cir. 1998)). Rouffet filed a patent application directed to technology to reduce signal transmission and receptor interruptions in the transmission signals from satellites. Rouffet taught changing the shape of the beam transmitted by the satellite's antenna to a fan-shaped beam. The Examiner rejected Rouffet's claims as unpatentable over U.S. patent number 5,199,672 (King) in view of U.S. Patent number 4,872,015 (Rosen) and a report titled "A Novel Non-Geostationary Staellite Communications System" (Ruddy).

In *Rouffet* the Court of Appeals found that:

> ***[b]ecause the Board did not explain the specific understanding or principle within the knowledge of a skilled artisan that would motivate one with no knowledge of Rouffet's invention to make the combination, this court infers that the examiner selected these references with the assistance of hindsight.*** This court forbids the use of hindsight in the selection of references that comprise the case of obviousness. See In re Gorman, 933 F.2d 982, 986, 18 U.S.P.Q. 2D (BNA) 1885, 1888 (Fed Cir. 1991). Lacking a motivation to combine references, the Board did not show a proper prima facie case of obviousness. This court reverses the rejection over the combination of King, Rosen, and Ruddy. (Emphasis added).

In re Rouffet at [*17].

Similarly, it is Applicants' position that the Examiner has used Applicants' invention as a blueprint to combine the references. The CAFC has ruled that "[a] holding that combination claims are invalid based merely upon finding similar elements in separate prior art patents would be 'contrary to statute and would defeat the congressional

purpose in enacting Title 35.' " *SmithKline Diagnostics*, 859 F.2d. at 886-887 (citing *Panduit Corp v. Dennison Mfg. Co.*, 810 F.2d 1561, 1577 (Fed. Cir. 1987)) (citations omitted).

Additional support of the position that the claimed invention is unobvious is found in *In re Vaeck* (*In re Vaeck* 947 F.2d 488. (Fed. Cir. 1991)) where the CAFC upheld the nonobviousness rejections of a biotechnology invention. In *Vaeck* the invention was drawn to "a chimeric (i.e., hybrid) gene comprising (1) a gene derived from a bacterium of the Bacillus genus whose product is an insecticidal protein, united with (2) a DNA promoter effective for expressing the Bacillus gene in a host cyanobacterium, so as to produce the desired insecticidal protein (footnote omitted)." *Id* at page 490. The prior art (a total of eleven references) was applied in various combinations against the claims. The primary reference (Dzelzkalns) taught the expression of a chimeric gene comprising a chloroplast promoter sequence fused to a gene encoding the enzyme chloramphenicol acetyl transferase (CAT) in cyanobacteria. The secondary references taught, *inter alia*, "expression of genes encoding certain *Bacillus* insecticidal proteins" in other host cells; "the initiation specificities *in vitro* of DNA-dependent RNA polymerases purified from two different species of cyanobacteria (footnote omitted);" and "a host-vector systems for gene cloning in the cyanobacterium." *Id* at page 491. The Examiner's position was that:

> it would have been obvious to one of ordinary skill in the art to substitute the Bacillus genes [which had been expressed in heterologous hosts in the teachings of the prior art] for the CAT gene in the vectors of Dzelzkalns in order to obtain high level expression of the Bacillus genes in the transformed cyanobacteria. The Examiner further contended that it would have been obvious to use cyanobacteria as heterologous hosts for expression of the claimed genes due to the ability of cyanobacteria to serve as transformed hosts for the expression of heterologous genes.

Id at page 492. The CAFC disagreed with the Examiner's position and found that the teachings of the prior art cited in *Vaeck* were not sufficient to support the interchangeability of bacteria and cyanobacteria as host organisms for the expression of heterologous insecticidal proteins. The court stated that "there is no suggestion in Dzelzkalns, the primary reference cited against all claims, of substituting in the disclosed plasmid a structural gene encoding Bacillus insecticidal proteins for the CAT gene utilized for selection purposes. The expression of antibiotic resistance-conferring genes in cyanobacteria, without more, does not render obvious the expression of unrelated genes in cyanobacteria." *Id* at page 493. The court further stated that while the prior art disclosed "expression of *Bacillus* genes encoding insecticidal proteins in certain transformed bacterial hosts, nowhere do these references disclose or suggest expression of such genes in transformed *cyanobacterial* hosts. . . . [w]hile it is true that bacteria and cyanobacteria are now both classified as procaryotes, that fact alone is not sufficient to motivate the art worker as the PTO contends. *Id* at pages 493 and 494.

The CAFC contrasted its findings in *In re Vaeck* with those in *In re O'Farrell* stating "[i]n contrast with the situation in *O'Farrell*, the prior art in this case offers no suggestion, explicit or implicit, of the substitution that is the difference between the claimed invention and the prior art." In *O'Farrell* the invention was directed to a "method for producing a predetermined protein in a stable form in a transformed host species of bacteria." *In re O'Farrell* 853 F.2d 894. 1988. 7 U.S.P.Q. 2d (BNA) 1673. The prior art (Polisky) taught a previous attempt to "control the expression of cloned heterologous genes inserted into bacteria." *Id* at page 899. The prior art differed from the claim at issue, however, because it taught a method of expressing "a segment of DNA from a frog that coded for ribosomal RNA," which is normally not translated into protein. Although ribosomal RNA is not normally translated into protein, the court found that in the prior art publication by Polisky the authors were "obviously interested in using their

approach to make heterologous proteins in bacteria." *Id* at page 900. The CAFC referred to the Polisky paper which stated:

> In fact, we have recently observed that induced cultures of pBGP123 contain elevated levels of [beta]-galactosidase of higher subunit molecular weight than wild-type enzyme (P. O'Farrell, unpublished experiments). We believe this increase results from translation of Xenopus [frog] RNA sequences covalently linked to [messenger] RNA for [beta]-galactosidase, resulting in a fused polypeptide.

Id at page 900 (quoting from Polisky et al. at page 4904). The court stated that "[t]he authors of the Polisky paper ***explicitly pointed out*** that if one were to insert a heterologous gene coding for a protein into their plasmid, it should produce a 'fused protein' consisting of a polypeptide made of beta-galactosidase plus the protein coded for by the inserted gene, joined by a peptide bond into a single continuous polypeptide chain." *Id* at page 901. The court also referred to a passage in the Polisky reference, where the authors stated that "[i]f an inserted sequence contains a ribosome binding site that can be utilized in bacteria, production of high levels of a readthrough transcript might allow for extensive translation of a functional eukaryotic polypeptide." Id at page 901 (quoting from Polisky et al.). The court upheld the PTO decision that the claims in *O'Farrell* were obvious over Polisky because:

> ***virtually everything in the claims was present in the prior art.*** . . . The main difference is that in Polisky the heterologous gene was a gene for ribosomal RNA while the claimed invention substitutes a gene coding for a predetermined protein. . . .Nevertheless, Polisky mentioned preliminary evidence that the transcript of the ribosomal RNA gene was translated into protein. Polisky further predicted that if a gene that codes for a protein were to be substituted for the ribosomal RNA gene, 'a readthrough transcript might allow for extensive translation of a functional eukaryotic polypeptide.' ***Thus, the prior art explicitly suggested the substitution that is the difference between the claimed invention and the prior art, and presented preliminary evidence suggesting that the***

> ***method could be used to make proteins***. (emphasis added).

Id at 901.

It is Applicants' position that, as in *In re Vaeck*, there is no teaching, either explicit nor implicit, in any of the references cited by the Examiner which would have impelled one of ordinary skill in the art to make the instantly claimed invention. The art cited by the Examiner is directed to individual elements of Applicants' invention, and not to the invention as a whole. Given the standard for obviousness set forth by the CAFC, it is Applicants' position that the Examiner has improperly relied on hindsight obtained from Applicants' invention in making the combination of references cited.

Applicants' unexpected Results Further Demonstrate That The Examiner Has Failed To Establish A *Prima Facie* Case Of Obviousness

Even assuming *arguendo* that a *prima facie* case of obviousness were established by the Examiner, (which Applicants dispute), the non-obviousness of the invention is apparent from the results achieved when the invention is put into practice. "One way for an Applicant to rebut a *prima facie* case of obviousness is to make a showing of 'unexpected results', i.e., to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." *In re Soni*, 54 F.23d 746, 34 USPQ2d 1684 (Fed. Cir. 1995).

In the instant application, Applicants show that administering a combination of PPI-1019, a β-amyloid derivative, and cyclosporin A, a P-glycoprotein inhibitor, results in not only an increased bioavailability of PPI-1019 to the brain of a subject, but also in a decrease in liver toxicity caused by this compound. By administering a P-glycoprotein inhibitor 30 minutes prior to the administration of a β-amyloid derivative, the bioavailability of the β-amyloid derivative is increased 5-fold in the brain (see figure 4) and the amount of β-amyloid derivative in the liver is decreased 6-fold (see figure 6) as compared to administration of only the β-amyloid derivative. The aforementioned decrease in the amount of β-amyloid derivative in the liver decreases the risk of hepatic injury to the subject.

It is, therefore, apparent that the actual results obtained through use of the instantly claimed invention are not predicted from (*i.e.*, are unexpected over) the teachings of the prior art.

In view of all of the foregoing, it is evident that the combination of the '868 application, Kroin *et al.* and the '980 application fail to teach or suggest the claimed invention. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this 35 U.S.C. § 103 rejection.

Rejection of Claims 24, 28, 30, 31 and 47 Under 35 U.S.C. § 102(a)

The Examiner has rejected claims 24, 28, 30, 31 and 47 under 35 U.S.C. § 102(a) as, "being anticipated by the WO Patent Application 99/10374." Specifically, the Examiner states that

> [t]he WO Patent Application '374 teaches conjugates of an Aβ-binding peptide and a cyclosporin A derivative. The conjugates, in combination with pharmaceutically acceptable carriers, are administered in vivo to treat neurological diseases. See, e.g., the Abstract; page 9, lines 23-30; and page 12, line 24- page 13, line 2. Because the same active agents are being administered by the same methods steps in the WO Patent Application '374 and in Applicants' claims, inherently the bioavailability of the Aβ-binding peptide of the WO Patent Application '374 will be enhanced by the cyclosporin of the WO Patent Application '374 to the same extent claimed by Applicants.

Applicants have cancelled claim 47 thereby rendering this rejection, as it pertains to claim 47, moot.

As this rejection pertains to claims 24, 25, 30 and 31, Applicants respectfully traverse the rejection for the following reasons. As amended, claims 24 and claims depending therefrom are directed to methods for enhancing the bioavailability of a β-amyloid peptide derivative to the brain of a subject, comprising administering to the subject the β-amyloid peptide derivative and a P-glycoprotein inhibitor, wherein the P-glycoprotein inhibitor and the β-amyloid polypeptide derivative are separate chemically distinct compounds and wherein the P-glycoprotein inhibitor is not a liposome or Tween-

80, thereby enhancing the bioavailability of the β-amyloid peptide derivative to the brain of the subject.

For a prior art reference to anticipate in terms of 35 U.S.C. §102 a claimed invention, the prior art must teach ***each and every element*** of the claimed invention. Lewmar Marine v. Barient, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

Applicants respectfully submit that the '374 application teaches ***conjugates*** of an Aβ-biding peptide and a cyclosporin A derivative (see, for example, page 8, line 28 through page 9, line 22 of the '374 specification). In contrast, the pending claims are directed to methods for enhancing the bioavailability of a β-amyloid peptide derivative to the brain of a subject in which separate, chemically distinct P-glycoprotein inhibitors and β-amyloid polypeptides derivative are administered to a subject. Accordingly, the pending claims are not anticipated by the '374 application and Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection.

Rejection of Claims 24, 28, 30, 31 and 47 Under 35 U.S.C. § 102(a)

The Examiner has rejected claims 24, 28, 30, 31 and 47 under 35 U.S.C. § 102(a) as, "being anticipated by the WO Patent Application 99/10374 as applied against claims above, and further in view of WO Patent Application 95/20980." Specifically, the Examiner is of the opinion that, "[t]he WO Patent Application '980 teaches that the cylcosporin of the WO Patent Application '374 is both a cytochrome P450 inhibitor and a P-glycoprotein inhibitor."

Applicants have cancelled claim 47 thereby rendering this rejection, as it pertains to claim 47, moot.

As this rejection pertains to claims 24, 25, 30 and 31, Applicants respectfully traverse the rejection for the following reason. As amended, claims 24 and claims depending therefrom are directed to methods for enhancing the bioavailability of a β-amyloid peptide derivative to the brain of a subject, comprising administering to the subject the β-amyloid peptide derivative and a P-glycoprotein inhibitor, wherein the P-glycoprotein inhibitor and the β-amyloid polypeptide derivative are separate chemically distinct compounds and wherein the P-glycoprotein inhibitor is not a liposome or Tween-

80, thereby enhancing the bioavailability of the β-amyloid peptide derivative to the brain of the subject.

For a prior art reference to anticipate in terms of 35 U.S.C. §102 a claimed invention, the prior art must teach ***each and every element*** of the claimed invention. Lewmar Marine v. Barient, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

As indicated above, the '374 application does not teach or suggest methods for enhancing the bioavailability of a β-amyloid peptide derivative to the brain of a subject in which separate, chemically distinct P-glycoprotein inhibitors and β-amyloid polypeptide derivatives are administered to a subject. Moreover, the '980 application fails to overcome the deficiencies of the '374 application.

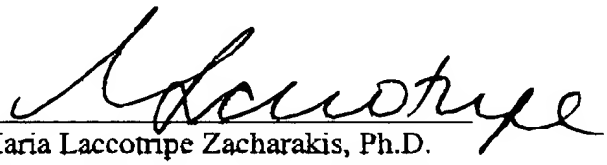
Accordingly, Applicants respectfully submit that the '374 and the '980 applications, alone or in combination, fail to teach or suggest the present invention and request that the Examiner reconsider and withdraw the foregoing rejection.

SUMMARY

Reconsideration and allowance of all the pending claims is respectfully requested.

If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the examiner is urged to call Applicants' Attorney at (617) 227-7400.

Respectfully submitted,



Maria Laccotripe Zacharakis, Ph.D.
Limited Recognition Under 37 CFR §10.9(b)
Attorney for Applicants

LAHIVE & COCKFIELD, LLP
28 State Street
Boston, MA 02109
Tel. (617) 227-7400
Dated: March 12, 2003

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

At page 3, lines 23-27, please insert the following re-written paragraph:

In a preferred embodiment, the drug whose bioavailability is enhanced, inhibits aggregation of natural β-amyloid peptide. In other preferred embodiments, the drug is an anti-cancer drug, *e.g.*, a chemotherapeutic agent; an anti-inflammatory agent, *e.g.*, nitric oxide, mannitol, allopurinol, or dimethyl sulfoxide; an anti-depressant; or a ~~cholinestarase~~ cholinesterase inhibitor.

In the claims:

24.**(Amended)** A method for enhancing the bioavailability of a β-amyloid peptide derivative to the brain of a subject, comprising administering to the subject the β-amyloid peptide derivative and a P-glycoprotein inhibitor, wherein said P-glycoprotein inhibitor and said β-amyloid polypeptide derivative are separate chemically distinct compounds and wherein said P-glycoprotein inhibitor is not a liposome or Tween-80, thereby enhancing the bioavailability of the β-amyloid peptide derivative to the brain of the subject.

25. **(Amended)** The method of claim 24, wherein the β-amyloid peptide derivative is selected from the group consisting of PPI-558, PPI-657, PPI-1019, PPI-578, ~~or~~ and PPI-655.

APPENDIX A

24. A method for enhancing the bioavailability of a β-amyloid peptide derivative to the brain of a subject, comprising administering to the subject the β-amyloid peptide derivative and a P-glycoprotein inhibitor, wherein said P-glycoprotein inhibitor and said β-amyloid polypeptide derivative are separate chemically distinct compounds and wherein said P-glycoprotein inhibitor is not a liposome or Tween-80, thereby enhancing the bioavailability of the β-amyloid peptide derivative to the brain of the subject.

25. The method of claim 24, wherein the β-amyloid peptide derivative is selected from the group consisting of PPI-558, PPI-657, PPI-1019, PPI-578, and PPI-655.

26. The method of claim 25, wherein the β-amyloid peptide derivative is PPI-1019.

27. The method of claim 24, wherein the P-glycoprotein inhibitor is valspodar.

28. The method of claim 24, wherein the P-glycoprotein inhibitor is cyclosporin A.

29. The method of claim 24, wherein the P-glycoprotein inhibitor is selected from the group consisting of antiarrhythmics, antibiotics, antifungals, calcium channel blockers, cancer chemotherapeutics, hormones, antiparasites, local anesthetics, phenothiazines, and tricyclic antidepressants.

30. The method of claim 24, further comprising administering to the subject a cytochrome P450 inhibitor.

31. The method of claim 24, wherein the β-amyloid peptide derivative and the P-glycoprotein inhibitor are administered simultaneously.

32. The method of claim 24, wherein the β-amyloid peptide derivative and the P-glycoprotein inhibitor are administered at different times.

COPY

We, Mark A. Findeis of Cambridge, Massachusetts, Kathryn Phillips of Boston, Massachusetts, Gary L. Olson of Mountainside, New Jersey, and Christopher Self of West Caldwell, New Jersey in consideration of One Dollar and other valuable consideration paid to us by

Praecis Pharmaceuticals Incorporated

a corporation of Delaware, having its principal place of business at One Hampshire Street, Cambridge, Massachusetts, the receipt of which is hereby acknowledged, do hereby sell, assign and transfer unto said

Praecis Pharmaceuticals Incorporated

its successors and assigns, the entire interest for the United States of America and all foreign countries including all rights of priority under the International Convention for the Protection of Industrial Property in a certain invention or improvement in

MODULATORS OF β-AMYLOID PEPTIDE AGGREGATION

described in an application

____ executed by us of even date herewith and about to be filed

__X__ Serial No. **09/519,019**, filed on **March 3, 2000** which is a continuation in part of Serial No.: 60/122,736, filed on March 4, 1999 in the United States Patent and Trademark Office, and in all Letters Patent of the United States and all foreign countries which may or shall be granted on said invention, or any parts thereof, or on said application, or any divisional, continuing, reissue or other applications based in whole or in part thereon. And we agree, for ourselves and our executors and administrators, with said corporation and its successors and assigns but at its or their expense and charges, hereafter to execute all applications, amended specifications, deed or other instrument, and to do all acts necessary or proper to secure the grant of Letters Patent in the United States and in all other countries to said corporation, with specifications and claims in such form as shall be approved by the counsel of said corporation and to vest and confirm in said corporation, its successors and assigns, the legal title to all such patents.

And we do hereby authorize and request the Commissioner of Patents and Trademarks of the United States to issue such Letters Patent as shall be granted upon said application or applications based thereon to said corporation, its successors and assigns.

WITNESS my hand and seal this 16TH day of June, 2000.

By: Gary L Olson
Gary L. Olson

State of New Jersey)
)ss
County of Morris)

Then personally appeared the above named Gary L. Olson and acknowledged the foregoing instrument to be his/her free act and deed, before me, this 16th day of June, 2000.

Notary Public
My commission expires:_____.

STEPHANIE Q. HUSH
NOTARY PUBLIC OF NEW JERSEY
My Commission Exp. Oct. 17, 2001
I. D. # 2194678

WITNESS my hand and seal this 16th day of June, 2000.

By: Christopher Self
Christopher Self

State of New Jersey)
)ss
County of Morris)

Then personally appeared the above named Christopher Self and acknowledged the foregoing instrument to be his/her free act and deed, before me, this 16th day of June, 2000.

Notary Public

My commission expires:_____.

STEPHANIE Q. HUSH
NOTARY PUBLIC OF NEW JERSEY
My Commission Exp. Oct. 17, 2001
I.D. # 2194678

WITNESS my hand and seal this 27th day of July, 2000.

By: Mark A. Findeis
Mark A. Findeis

State of MASS.)
)ss
County of Middlesex)

Then personally appeared the above named Mark A. Findeis and acknowledged the foregoing instrument to be his/her free act and deed, before me, this 27 day of July, 2000.

Notary Public

My commission expires: 3/1/06.

WITNESS my hand and seal this 27 day of July, 2000.

By: Kathryn Phillips
Kathryn Phillips

State of MASS)
)ss
County of Middlesex)

Then personally appeared the above named Kathryn Phillips and acknowledged the foregoing instrument to be his/her free act and deed, before me, this 27th day of July, 2000.

Notary Public

My commission expires: 3/1/06.

COPY

APPENDIX C

ASSIGNMENT

We, Neil J. Hayward of North Grafton, MA and Malcolm L. Gefter of Lincoln, MA in consideration of One Dollar and other valuable consideration paid to us by

Praecis Pharmaceuticals Inc.

a corporation of Delaware, having its principal place of business at 830 Winter Street, Waltham, Massachusetts, the receipt of which is hereby acknowledged, do hereby sell, assign and transfer unto said

Praecis Pharmaceuticals Inc.

its successors and assigns, the entire interest for the United States of America and all foreign countries including all rights of priority under the International Convention for the Protection of Industrial Property in a certain invention or improvement in

METHODS FOR ENHANCING THE BIOAVAILABILITY OF A DRUG

described in an application

___ executed by us of even date herewith and about to be filed

__X__ Serial No. 09/781,133, filed on February 9, 2001

in the United States Patent and Trademark Office, and in all Letters Patent of the United States and all foreign countries which may or shall be granted on said invention, or any parts thereof, or on said application, or any divisional, continuing, reissue or other applications based in whole or in part thereon. And we agree, for ourselves and our executors and administrators, with said corporation and its successors and assigns but at its or their expense and charges, hereafter to execute all applications, amended specifications, deed or other instrument, and to do all acts necessary or proper to secure the grant of Letters Patent in the United States and in all other countries to said corporation, with specifications and claims in such form as shall be approved by the counsel of said corporation and to vest and confirm in said corporation, its successors and assigns, the legal title to all such patents.

And we do hereby authorize and request the Commissioner of Patents and Trademarks of the United States to issue such Letters Patent as shall be granted upon said application or applications based thereon to said corporation, its successors and assigns.

WITNESS my hand and seal this _____ day of _____, 2001.

By: _____
Neil J. Hayward

State of)
)ss
County of)

Then personally appeared the above named Neil J. Hayward and acknowledged the foregoing instrument to be his/her free act and deed, before me, this ____ day of _____, 2001.

_____
Notary Public
My commission expires: _____.

WITNESS my hand and seal this 30th day of January, ~~2001~~ 2002 LMS

By: _____
Malcolm L. Gefter

State of MASS.)
)ss
County of Norfolk)

Then personally appeared the above named Malcolm L. Gefter and acknowledged the foregoing instrument to be his/her free act and deed, before me, this 30th day of January, ~~2001~~ 2002 LMS

_____
Notary Public

My commission expires: 3/31/06.

ASSIGNMENT

We, Neil J. Hayward of North Grafton, MA and Malcolm L. Gefter of Lincoln, MA in consideration of One Dollar and other valuable consideration paid to us by

Praecis Pharmaceuticals Inc.

a corporation of Delaware, having its principal place of business at 830 Winter Street, Waltham, Massachusetts, the receipt of which is hereby acknowledged, do hereby sell, assign and transfer unto said

Praecis Pharmaceuticals Inc.

its successors and assigns, the entire interest for the United States of America and all foreign countries including all rights of priority under the International Convention for the Protection of Industrial Property in a certain invention or improvement in

METHODS FOR ENHANCING THE BIOAVAILABILITY OF A DRUG

described in an application

___ executed by us of even date herewith and about to be filed

__X__ Serial No. 09/781,133, filed on February 9, 2001

in the United States Patent and Trademark Office, and in all Letters Patent of the United States and all foreign countries which may or shall be granted on said invention, or any parts thereof, or on said application, or any divisional, continuing, reissue or other applications based in whole or in part thereon. And we agree, for ourselves and our executors and administrators, with said corporation and its successors and assigns but at its or their expense and charges, hereafter to execute all applications, amended specifications, deed or other instrument, and to do all acts necessary or proper to secure the grant of Letters Patent in the United States and in all other countries to said corporation, with specifications and claims in such form as shall be approved by the counsel of said corporation and to vest and confirm in said corporation, its successors and assigns, the legal title to all such patents.

And we do hereby authorize and request the Commissioner of Patents and Trademarks of the United States to issue such Letters Patent as shall be granted upon said application or applications based thereon to said corporation, its successors and assigns.

WITNESS my hand and seal this 23rd day of January, ~~2001~~ 2002

By: N. Hayward.
Neil J. Hayward

State of Massachusetts)
)ss
County of Middlesex)

Then personally appeared the above named Neil J. Hayward and acknowledged the foregoing instrument to be his/her free act and deed, before me, this 23rd day of January, ~~2001~~ 2002

Frank H. Lipsitz
Notary Public
My commission expires: FRANK H. LIPSITZ
Notary Public
My Commission Expires
January 27, 2006

WITNESS my hand and seal this _____ day of _____, 2001.

By: _____
Malcolm L. Gefter

State of)
)ss
County of)

Then personally appeared the above named Malcolm L. Gefter and acknowledged the foregoing instrument to be his/her free act and deed, before me, this _____ day of _____, 2001.

_____
Notary Public

My commission expires: _____.